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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/009,950 | 12/14/2001 | Akira Nakamura | 31671-176197 | 7278 |

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VENABLE LLP
P.O. BOX 34385
WASHINGTON, DC 20045-9998

| EXAMINER | |
|---|---|
| BERTOGLIO, VALARIE E | |
| **ART UNIT** | **PAPER NUMBER** |
| 1632 | |

DATE MAILED: 09/30/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/009,950 | NAKAMURA ET AL. | |
| | Examiner | Art Unit | |
| | Valarie Bertoglio | 1632 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *22 August 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1 and 3* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 3* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *12/14/2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

Applicant's Appeal Brief dated 08/22/2005 has been received. After further consideration, the finality of the office action dated 03/23/2005 is withdrawn.

Claims 1 and 3 have been amended, are pending, and are under consideration.

It is noted that the Appeal Brief dated 08/22/2005 is not in compliance with 37 CFR 41.37. Specifically, the heading "Summary of the Invention" at page 2 should read "Summary of claimed subject matter". Furthermore, no Evidence Appendix or Related Proceedings Appendix is included. If no content for such appendices exists, empty appendices should be provided to indicate such.

### *Claim Rejections - 35 USC § 112-1st paragraph*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The rejection of claims 1 and 3 under 35 U.S.C. 112, first paragraph, enablement is withdrawn. Because the claims require inactivation of the FcγRIIB gene and one of skill in the art would know how to determine if a genetic mutation results in inactivation, the enablement requirement is met. However, the terms deficiency and substitution are defined by the specification and pose grounds of rejection under 35 USC 112, 2nd paragraph as set forth below.

### *Claim Rejections - 35 USC § 112-2nd paragraph*

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1 and 3 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 3 are unclear because of the term "substitution" at line 5 of claim 1 and at line 9 of claim 3.It is unclear if the term substitution is referring to substitution of the gene with another gene or mutation of the gene by substitution of a single nucleotide.

The term "deficiency" in claims 1 and 3 is a term which renders the claim indefinite. The term is not defined by the specification and it is not clear if the claim is referring to a total lack of the gene (i.e. a gene deletion) or a deficiency of a part of the gene. Furthermore, a deficiency is a result of a genetic mutation, not a type of mutation itself. Types of mutation include deletion, translocation, substitution, inversion and the like.

It is noted that the claims require that the FcγRIIB be inactivated, rendering the phrase "such as destruction, deficiency, or substitution" superfluous.

Claim 3 is unclear because of the term "amount" in line 18 because it is not clear whether the term is referring to the degree of severity of each symptom or the number of symptoms present at any degree of severity wherein the symptoms are diffuse alveolar hemorrhage, glomerulonephritis and appearance of antikidney glomerular basement membrane. It is noted that the preamble is drawn to "improving symptoms".

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The previous rejection of claim 1 under 35 U.S.C. 103(a) is withdrawn in favor of the following rejection.

Claims 1 and 3 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kalluri et al (Nov. 1997, **J. Clin. Invest**, 100:2263-2275) and Kalluri (1994, PNAS, Vol. 91, pages 6201-6205;IDS) and Abbate (1998, Kidney International, Vol. 54, pages 1550-1561; IDS), in view of Takai (1996, Nature, Vol. 379, pages 346-348; IDS) and Yuasa et al (Jan. 1999, J Exp Med, 189:187-194), further in view of Kulluri et al (1995, **J Am Soc Nephrol**, 6:1178-1185).

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim 1 is drawn to a mouse model of Goodpastures syndrome wherein the genome of the mouse comprises a homozygous disruption of the FcγRIIB gene and upon immunization with type IV collagen the mouse exhibits diffuse alveolar hemorrhage, glomerulonephritis and the appearance of antikidney glomerular basement membrane antibody. Claim 3 is drawn to a method of using the mouse to screen for remedies of for improving symptoms of diffuse alveolar hemorrhage, glomerulonephritis and appearance of antikidney glomerular basement membrane antibody.

Kalluri et al (1997) taught immunizing various strains of wild-type mice with the α3(IV) NC1 antigen from type IV collagen (page 2264, col. 2, paragraph 5) leading to high titers of α3(IV) NC1 antibodies that bind to the type IV collagen in kidney basement membrane and lungs (page 2264, col. 2,last paragraph; paragraph bridging pages 2266-2267). Some strains (SJL, for example) exhibited severe glomerulonephritis and focal to massive alveolar hemorrhage (page 2265, col. 1, paragraph 2). Similarly, Abbate taught immunizing wild-type rats with α3 type IV collagen causing experimental Goodpastures syndrome characterized by pulmonary hemorrhage involving alveolar capillaries, crescentic glomerulonephritis, deposits of IgG along glomerular basement membranes (for example, see page 1560, col. 1, last para.). Kalluri (1994) taught immunizing rabbits with the NC1 subdomain of α3 type IV collagen causing formation of autoantibodies that lead to a mimicking of human Goodpastures syndrome (page 6201, col. 1; page 6203, paragraph bridging columns). Kalluri also taught using the mouse to test for new forms of therapy (page 6205, col. 1, paragraph 2). Neither Kalluri (1997) nor Abbate not Kalluri (1994) taught using an FcγRIIB knockout mouse in making a model of Goodpastures or using type IV collagen rather than subunits of type IV collagen.

However, Takai taught knocking out the FcγRIIB gene in mice results in increased humoral and anaphylactic responses in the mice in response to antigens including sheep red blood cell, trinitrophenol keyhole limpet haemocyanin and trinotrophenol lipopolysachharide or TNP-Ficoll. Takai taught that the FcγRII gene encodes a low-affinity immunoglobulin-G receptor that acts as a general negative regulator of immune-complex triggered immune system activation. Loss of this negative-regulator increased humoral and anaphylactic responses in the mice because the mice lack ability for regulation of antibody level in response to antigenic

stimulation (page 347, col. 1, last paragraph). Furthermore, Yuasa taught that the FcγRIIB knockout mice of Takai exhibited collagen induced arthritis in response to immunization of type II collagen, further exemplifying the role of autoimmune suppression by FcγRIIB and the enhancement of such a reaction as a result of FcγRIIB gene disruption. Neither Yuasa nor Takai taught immunizing FcγRIIB-deficient mice with type IV collagen.

Furthermore, Kalluri (1995) taught that antisera from some Goodpasture's patients also bind to α1(IV) collagen and α4(IV) collagen in addition to α3(IV) collagen (page 1183, col. 1, paragraphs 1-2) that was used as antigen by Kalluri (1994), by Abbate and by Kalluri (1997).

It would have been obvious to one of skill in the art at the time the application was filed to immunize the FcγRIIB knockout mice taught by Takai and by Yuasa with a type IV collagen antigen as taught by Kalluri (1994), by Abbate and by Kalluri (1997). One of skill in the art would have been motivated to combine the teachings of Yuasa, Takai, Kalluri (1994), Abbate, and Kalluri (1997) because it was known that type IV collagen is an antigen known to cause the auto-immune reactivity responsible for Goodpastures syndrome (as taught by Kalluri (1994 and 1997) and by Abbate) and that the FcγRIIB knockout mice lack a negative regulatory response to various antigens that contribute to the development of autoimmunity and can cause an enhanced autoimmune response in animal upon immunization with a known auto-immune antigen (Yuasa). Thus, the combination of the FcγRIIB knockout mouse with the immunization with type IV collagen allows for mouse model of Goodpastures syndrome known to have greater autoimmune-reactivity, a characteristic of human Goodpastures syndrome. Previous models using wild-type animals demonstrated weaker phenotypes (see Kalluri, 1997, page 2263, col. 1, paragraph 3). One of skill in the art at the time the invention was made would have been

motivated to use all subunits of type IV collagen rather than the α3(IV) collagen subunit because Kalluri (1995) demonstrated that some Goodpastures patients also produced antibody to the α1(IV) and α4(IV) collagen subunits and the full α4(IV) collagen would present more antigenic epitopes. It was desired, at the time of filing, to produce a model with greater disease severity and therefore one would have been motivated to use the FcγRIIB knockout in combination with collagen antigen comprising more antigenic components. It also would have been obvious to use the mouse to screen for remedies using the claimed method steps because it is generally known in the art to use disease models to screen for therapies and to use the claimed method steps that are merely steps of the scientific method. One would have been motivated to use the disease model in light of the art accepted motivation to make and use animal disease models for the purpose of determining new therapies and because Kalluri (1994) suggests using the mouse to determine efficacy of new treatments (page 6205, col. 1, paragraph 2).

One of skill in the art at the time the invention was made would have had a reasonable expectation of success in combing the above teachings because the reagents were known in the art, wild-type mice could be made to exhibit the desired symptoms due to an autoimmune reaction and the knockout mice were known in the art to exhibit heightened symptoms and autoimmune reaction to other collagen types that are subject to autoimmune reaction (i.e. type II collagen and rheumatoid arthritis).

Thus, the claimed invention is clearly *prima facie* obvious in the absence of evidence to the contrary.

***Conclusion***

**No claim is allowed.**

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Valarie Bertoglio whose telephone number is (571) 272-0725. The examiner can normally be reached on Mon-Thurs 5:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

RAM R. SHUKLA, PH.D.
SUPERVISORY PATENT EXAMINER

Valarie Bertoglio
Examiner
Art Unit 1632

SCOTT D. PRIEBE, PH.D
PRIMARY EXAMINER